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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/919,196	07/31/2001	Ming-Fong Lin	UNMC.63157	3974

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	11

DATE MAILED: 10/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/919,196	LIN, MING-FONG	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-11* is/are pending in the application.

4a) Of the above claim(s) *5-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claim 4.

Accordingly, claims 1-3 are being examined.

The following are the remaining rejections.

DECLARATION

Applicant submits a Declaration by Dr. Ming-Fong Lin stating that the biochemical properties and the phenotype of claimed terminally differentiated cell lines are irreversible. The submission of the Declaration is acknowledged and entered.

In view of the Declaration, the rejection under 112, first paragraph, scope of the previous Office action has been withdrawn.

DEPOSIT REQUIREMENT

Objection of the specification and rejection of claims 2-3 under 112, first paragraph remain for reasons already of record in paper No:7.

Applicant argues that the claimed cell lines NE-1-3 and NE-1-8 have been deposited with ATCC under the Budapest Treaty, as shown by the attached deposit form. Applicant further argues that the ATCC accession number, the date of the deposit, and the name and address of the depository have been provided at page 10, lines 7-15 of the specification.

Rejection remains, because the specification fails to provide an affidavit or declaration stating that all restrictions upon public access to the deposits will be irrevocably removed upon the granting of a patent on this application, and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required.

See 37 CFR 1.803-1.809 for explanation of these requirements.

OBJECTION

Claim 1 is objected to for the use of the language "associated". It is not clear how the NE-like cell line is associated with prostate cancer.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION, NEW REJECTION

Claims 1-3 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 1-3 are drawn to a human prostate cancer-associated neuroendocrine (NE)-like cell line (claim 1). Said cell line is NE-1-3, deposited at ATCC under accession number PTA-3568 (claim 2) or NE-1-8, deposited at ATCC under accession number PTA-3569 (claim 3).

The specification disclose that "NE-like" cells refers to a population of cells derived from LNCaP human prostate cancer cells following long term-culture in an androgen-dependent-depleted conditions. The specification further discloses isolation of

a single survival cell under androgen-depleting conditions, and sucloned into three cell lines NE-1-3, NE-1-8 and NE-1-9, having the characteristic neuronal cell morphology, i.e. cell bodies with long, irregular neurite like processes. The specification discloses that the three suclone cell lines NE-1-3, NE-1-8 and NE-1-9 have the following markers: a) NE-specific markers, such as neuron-specific enolase (NSE), b) the marker neurotensin, associated with a variety of cancers, c) the receptor-type protein tyrosine phosphatase alpha (RPTP alpha), the increased expression of which is correlated with an increased level of NSE, and d) ErbB-2, related to growth regulation, all expressed at a higher level than those expressed in the parent LNCaP, whereas the growth related marker EGFR is decreased as compared to that expressed in the parent LNCaP (Example 1, pages 10-17).

The specification discloses that expression of androgen receptor and prostate specific antigen is completely suppressed in all three subclone NE-like cell lines, as compared to those expressed in the parent LNCaP (p.13, second paragraph).

The specification discloses that the NE cells from normal prostate gland are terminally differentiated and do not proliferate, whereas the NE-like cell lines are capable of proliferating under steroid-reduced conditions (p.13).

It is noted that from the definition of "NE-like" cells in the specification, "NE-like" cells in claim 1 comprise any LNCaP human prostate cancer cell with any chromosome characteristics, or having any property, provided it has been exposed to long term-culture in androgen-depleted conditions.

One cannot determine whether the claimed genus of NE-like cell lines would have the same chromosomal constituents or properties as those of the single cloned survival cell described in the specification. It is noted that it is well known in the art that different cell lines have different and unique properties and chemical identity. It is also well known in the art that a property of a cell line could change with long-term culture, due to culture artifact, and thus one cannot determine whether under long-term culture with androgen-depleted conditions, different cells with different chromosomal constituents or properties could survive and be cloned, which do not necessarily have the same chromosomal constituents or properties as those of the single cloned survival cell described in the specification. For example, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). Mustafa Ozen et al, 1996, Intl J Oncology, 8(5): 883-888, teach that prostate cells in late culture all show numerous changes in chromosome 5 in addition to some new markers. The evidence presented clearly demonstrates that in cell culture systems, in general, and in cancer derived cell

lines in particular, that artifactural chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays. In other words, one cannot determine whether the claimed genus of NE-like cell lines would have the same chromosomal constituents or properties as those of the single cloned survival cell described in the specification.

Further, the structural properties such as chromosomal constituents of the claimed cell lines, including NE-1-3 and NE-1-8, are not adequately described in the specification. It is well known in the art that cross-contamination of different cell lines is a longstanding and widespread problem, and authentication and standardization by techniques such as short tandem repeat profiling is usually necessary to identify a cell line (Masters, J R et al, PNAS, USA, 2001, 98(14): 8012-8017). Thus based on the disclosure in the specification, one cannot determine whether the claimed NE-like cell lines, including NE-1-3 and NE-1-8 are derived from the authentic LNCaP. In other words, the structural properties such as chromosomal constituents of the claimed cell lines, including NE-1-3 and NE-1-8, are not adequately described in the specification.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure,

formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-

Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here.

Thus, the instant specification may provide an adequate written description of the claimed genus of NE-like cell lines derived from LNCaP human prostate cancer cells following long term-culture in an androgen-dependent-depleted conditions, per Lilly by structurally describing a representative number of NE-like cell lines derived from LNCaP human prostate cancer cells following long term-culture in an androgen-dependent-depleted conditions or by describing "structural features, such as chromosomal characteristics, or short tandem repeat profiles that are commonly used to characterize cell lines (Masters, J R et al, PNAS, USA, 2001, 98(14): 8012-8017), common to the members of the genus, which features constitute a substantial portion of the genus." Similarly, the instant specification may provide an adequate written description of the claimed NE-1-3 and NE-1-8, per Lilly by describing "structural features", such as chromosomal characteristics, or short tandem repeat profiles that are commonly used to characterize cell lines. Alternatively, per Enzo, the specification can show that the

claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe the required NE-like cell lines to practice claims 1-3 in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any NE-like cell line, nor does the specification provide any partial structure of such NE-like cell lines, nor any physical or chemical characteristics of the NE-like cell lines, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses a single surviving cell in androgen-depleting culture conditions, which gives rise to three subclones cell lines NE-1-3, NE-1-8 and NE-1-9 in Example 1, on pages 10-17, this does not provide a description of the claimed NE-like cell lines that would satisfy the standard set out in Enzo.

The specification also fails to describe the NE-like cell lines the test set out in Lilly. The specification describes only three subclones from a single surviving LNCaP cell under androgen-depleted conditions. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Moreover, although claims 2-3 recite the claimed NE-1-3 and NE-1-8 accompanied by a deposit accession number, a deposit is not a substitute for a written

description, according to MPEP 2163 (R-1). "The description must be sufficient to permit verification that the deposited biological material is in fact that disclosed. Once the patent issues, the description must be sufficient to aid in the resolution of questions of infringement." Id. at 34,880.). Such a deposit is not a substitute for a written description of the claimed invention. The written description of the deposited material needs to be as complete as possible because the examination for patentability proceeds solely on the basis of the written description. See, e.g., In re Lundak, 773 F.2d 1216, 227 USPQ 90 (Fed. Cir. 1985). See also 54 FR at 34,880 ("As a general rule, the more information that is provided about a particular deposited biological material, the better the examiner will be able to compare the identity and characteristics of the deposited biological material with the prior art.".

Thus, the specification does not provide an adequate written description of the NE-like cell lines that is required to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1 is drawn to a human prostate cancer-associated neuroendocrine (NE)-like cell line. Claims 2-3 are drawn to prostate cancer associated cell line cell line NE-1-

3, deposited at ATCC under accession number PTA-3568 (claim 2) or NE-1-8, deposited at ATCC under accession number PTA-3569 (claim 3).

The disclosure in the specification has been set forth above.

1. It is noted that from the definition of "NE-like" cells in the specification, "NE-like" cells in claim 1 comprise any LNCaP human prostate cancer cell with any chromosome characteristic, or having any property, provided it has been exposed to long term-culture in androgen-depleted conditions.

As drawn to claim 1, one cannot extrapolate the teaching of a single cell clone giving rise to subclones NE-1-3, NE-1-8 and NE-1-9 in the specification to the claimed cell lines of claim 1. It is well known in the art that different cell lines have different and unique properties and chemical identity. It is also well known in the art that a property of a cell line could change with long-term culture, due to culture artifact, and thus one cannot determine whether under long-term culture with androgen-depleted conditions, different cells with different chromosomal constituents or properties could survive and be cloned, which do not necessarily have the same chromosomal constituents or properties as those of the single cloned survival cell described in the specification. For example, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu

(in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). Mustafa Ozen et al, 1996, Intl J Oncology, 8(5): 883-888, teach that prostate cells in late culture all show numerous changes in chromosome 5 in addition to some new markers. The evidence presented clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactural chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays. In other words, one cannot predict that the claimed of NE-like cell lines would have the same chromosomal constituents or properties as those of the single cloned survival cell described in the specification.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

2. Further, as drawn to claims 1-3, claims 1-3 are not enabled, because it is unpredictable that the claimed cell lines are associated with prostate cancer, and thus could be practically useful, e.g. for treating prostate cancer. It is well known in the art that inter- and intraspecies cross-contamination of different cell lines is a longstanding and widespread problem (Masters, J R et al, PNAS, USA, 2001, 98(14): 8012-8017) For example, breast cancer cells could be mistakenly used in liver cancer research, or cells from hamsters and rabbits could have been labeled as coming from human. Masters et al teach that authentication and standardization by techniques such as short tandem

repeat profiling is usually necessary to identify a cell line (Masters, J R et al, PNAS, USA, 2001, 98(14): 8012-8017).

The specification only discloses the properties of the claimed cell lines based on expression of some markers as compared to the parent LNCaP. However there is no disclosure whether the parent LNCaP cell line, or the subclones NE-1-3, NE-1-8, have been authenticated. Thus, based on the disclosure in the specification, one cannot determine whether the claimed NE-like cell lines, including NE-1-3 and NE-1-8 are derived from the authentic LNCaP, i..e a prostate cancer cell line or are associated with prostate cancer. In other words, since the structural properties such as chromosomal constituents of the claimed cell lines, including NE-1-3 and NE-1-8, are not adequately described in the specification, one cannot predict that the claimed cell lines are actually derived from a prostate cancer cell line, or are in any way associated with prostate cancer, and thus one would not know how to use the claimed invention.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone

number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS
October 03, 2003

SUSAN UNGAR, PH.D
PRIMARY EXAMINER